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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,923	07/19/2005	Cedric Szpirer	VANM290.001APC	6813

20995 7590 05/28/2009

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ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
05/28/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/507,923	SZPIRER ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16 and 18-42* is/are pending in the application.

4a) Of the above claim(s) *19-21,29-33 and 37-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,16,18,22-28,34-36,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *June 10, 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant has elected without traverse the invention of Group I, Claims 15-24 and 26-28, drawn to a recombinant cell or organism having incorporated into genome i) a genetic construct a nucleotide sequence encoding a toxic molecule, and ii) a genetic sequence encoding an antidote molecule to said toxic molecule.

Within Group I, Applicant has elected with traverse the following restricted embodiments:

i) wherein the toxic molecule is ccdB, as recited in claim 18,
ii) wherein the biological organism is a yeast, as recited in claim 22,
iii) wherein the non-toxic compound is an exogenous compound, as recited in claim 24,
iv) wherein the cell compartment comprising a genome within which the genetic construct is integrated is a chloroplast, as recited in claim 27, and
v) wherein the selectable marker is bordered by two different toxic genes, as recited in claim 28.

Examiner's Note

1. **A decision of the petition under 37 C.F.R. 1.144 filed June 10, 2008 has been rendered**, paper entered April 28, 2009, whereupon the petition has been granted-in-part.

The restriction requirement between elected Group I and non-elected Group II is withdrawn.

The restriction requirement between elected Group I/II and non-elected Group III is maintained.

The species election requirement wherein the genetic construct does not or does not comprise a selectable marker, as recited in claim 15(i), is withdrawn.

The species election requirement wherein the genetic sequence encoding the antidote is not added to the construct, as recited in claim 15(ii), is withdrawn.

The species election requirement wherein Applicant has elected the toxic molecule ccdB recited in claim 18, is maintained.

The species election requirement wherein the requirement to elect a biological organism from the groups of organism of plant, animal, mammal, insect or yeast has been reformatted as a requirement to elect a plant, animal or yeast. Applicant elected the yeast recited in claim 22.

The species election requirement wherein the non-toxic compound is an exogenous compound or synthesized by the eukaryotic host cell is maintained. Applicant elected an exogenous compound recited in claim 24.

The species election requirement wherein the cell compartment comprising a genome within which the genetic construct is integrated is maintained. Applicant elected the chloroplast recited in claim 27.

The species election requirement wherein the selectable marker is bordered by two different or identical toxic genes recited in claim 28 is maintained. Applicant elected "two different toxic genes".

The restriction requirement is therefore made FINAL.

Amendments

In the reply filed June 10, 2008, Applicant has cancelled Claims 1-14 and 17, withdrawn Claims 19-21, 25, 28-34 and 36-40, amended Claims 15-16, 18-21, 23-28 and 34-40, and added new claims, Claims 41-42.

The amendment filed June 10, 2008 is objected to for failing to comply with MPEP §1.121 Manner of making amendments in applications.

(c) Claims. Amendments to a claim must be made by rewriting the entire claim with all changes (e.g., additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

(1) Claim listing. All of the claims presented in a claim listing shall be presented in ascending numerical order. Consecutive claims having the same status of "canceled" or "not entered" may be aggregated into one statement (e.g., Claims 1-5 (canceled)). The claim listing shall commence on a separate sheet of the amendment document and the sheet(s) that contain the text of any part of the claims shall not contain any other part of the amendment.

(2) When claim text with markings is required. All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended," and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended," or "withdrawn" if also being amended, shall include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn- currently amended."

In the instant case, Claims 19-21, 25, 28, 34 and 36-40 at the time of Applicant's response should have been annotated (Withdrawn, Currently Amended).

Claims 19-21, 29-33 and 37-40 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 15-16, 18, 22-28, 34-36 and 41-42 are under consideration.

Priority

This application is a 371 of PCT/BE03/00045, filed March 19, 2003. Applicant's claim for the benefit of a prior-filed parent provisional application 60/365,938, filed on March 19, 2002 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

The disclosure of the prior-filed application, 60/365,938, filed on March 19, 2002, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, 60/365,938 does not support claim 27, wherein the genetic construct is integrated into the genome of a specific cell compartment, specifically a chloroplast. Rather, the provisional application discloses integration into the nuclear genome. A certified copy of PCT/BE03/00045 has not been filed with the instant application so as to allow the Examiner to ascertain whether claim 27 is supported as of March 19, 2003. Accordingly, the effective priority date of claim 27 is granted as the filing date of the instant application, July 19, 2005. If Applicant believes the earlier applications provide support for this disclosure, Applicant should point out such support by page and line number in the reply to this Action.

Claims 15-18, 22-24, 26, 28 and 35 are supported by the disclosure of 60/365,938, filed on March 19, 2002. Accordingly, the effective priority date of claims 15-18, 22-24, 26, 28 and 35 is granted as March 19, 2002.

Response to Arguments

Applicant argues that support for claim 27 may be found in 60/365,938, last sentence on page 4.

Applicant's argument(s) has been fully considered, but is not persuasive. The last paragraph discloses the introduction of a gene coding for a poison target, e.g. gyrase, wherein the last sentence discloses the poison target may be guided to specific cell compartments, e.g. the chloroplast. However, the instant claim does not recite that the gene product, e.g. gyrase, be guided to a specific cell compartment. Rather, the claim recites that the genetic construct is integrated into the genome of a specific cell compartment, i.e. the chloroplast. Targeting a protein to a specific cellular compartment is not the same as directing the integration of a nucleic acid vector into an organelle genome [integrated into the genome of a specific cell compartment].

The Examiner has found support for the instant claim 27 in the specification [0046] of PCT/BE03/0004, as indicated by Applicant. Accordingly, the effective priority date of claim 27 is granted as March 19, 2003. If Applicant believes 60/365,938 provides support for this disclosure, Applicant should point out such support by page and line number in the reply to this Action.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on June 10, 2008 that has been considered. The signed and initialed PTO Form 1449 is mailed with this action.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the June 10, 2008 response will be addressed to the extent that they apply to current rejection(s).

Claim Objections

2. **The prior objection to Claim 18 is withdrawn** in light of Applicant's amendment to the claim to first identify the toxic gene by its complete name prior to using its acronym.

Claim Rejections - 35 USC § 101

3. **The prior rejection of Claims 15-16, 18, 22-24, 26-27 and 35 under 35 U.S.C. 101 is withdrawn** in light of Applicant's argument that the statement of utility is credible because the specification provides detailed instructions as to how to make such recombinant cells and how to use such cells for site specific integration of an exogenous nucleic acid sequence [0018], which the Examiner finds persuasive. An Applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement. MPEP §2107.

Claim Rejections - 35 USC § 112

4. **The prior rejection of Claims 15-16, 18, 22-24, 26-27 and 35 under 35 U.S.C. 112, first paragraph,** as failing to comply with the written description requirement, **is withdrawn** in light of Applicant's amendment to the claims and the argument that most of the poison/antidote pairs were known at the time of fling the instant application, e.g. the partners of ParE, RelE and MazE, are ParD, RelB and MazF, respectively. Thus, a sufficient representative number of examples of poison/antidote systems are known in the art. The Examiner finds this argument persuasive.

5. **The prior rejection of Claims 15-16, 18, 22-24, 26-27 and 35 under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement, **is withdrawn** in light of Applicant's amendment to the claims and the argument that most of the poison/antidote pairs were known at the time of fling the instant application, e.g. the partners of ParE, RelE and MazE, are ParD, RelB and MazF, respectively. Thus, a sufficient representative number of examples of poison/antidote systems are known in the art. The Examiner finds this argument persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

6. **The prior rejection of Claims 15-16, 18, 22-24, 26-27 and 35 under 35 U.S.C. 112, second paragraph**, **is withdrawn** in light of Applicant's argument that the phrase "a poison protein selected from a poison/antidote group" means "a poison protein selected from a set of proteins comprising poison/antidote protein pairs, and that the artisan would clearly understand what is meant by "a poison protein," "an antidote molecule to said poison protein" and a "poison/antidote group." Furthermore, the artisan would understand that the term "not native" would clearly mean an antidote molecule that does not naturally occur in the cell. The Examiner finds these arguments persuasive.

7. **Claim 28 is rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

This is new rejection.

Claim 28 recites the limitation "the selectable marker" in reference to Claim 15. There is insufficient antecedent basis for this limitation in the claim because Claim 15 does not recite that genetic construct comprising a genetic sequence encoding a poison protein necessarily comprises a sequence encoding a selectable marker.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the Applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the Applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the Applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. **Claims 15-16, 18, 22-24, 26 and 35 stand, and Claims 25, 28, 34, 36 and 41-42 are newly rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e)** as being anticipated by Norris et al (U.S. Patent No. 6,271,359).

The Examiner provides Sandmeyer et al (Ann. Rev. Genetics 24:491-518, 1990; Abstract only) and Yanofsky et al (Cell 47(3):471-477, 1986; Abstract only) as evidentiary references.

This rejection is maintained for reasons of record in the Office Action mailed December 12, 2007 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed June 10, 2008 and the petition decision dated April 28, 2009.

With respect to claim 15, Norris et al disclose eukaryotic cells comprising a genetic construct comprising at least one nucleotide sequence comprising a toxic gene, wherein said toxic gene is under the control of an inducible promoter, the eukaryotic cell further comprising an anti-toxic genetic sequence encoding an antidote molecule to the poison protein, wherein said antidote molecule is a heterologous ("not natively present") in said eukaryotic cell (col. 8, lines 35-39; col. 30, lines 46-50).

With respect to claim 16, the genetic sequence encoding the antidote molecule is under the control of an inducible promoter/operator genetic sequence (col. 6, lines 15-24; col. 8, lines 35-37; col. 29, lines 45-53).

With respect to claim 18, the toxic gene is CcdB (col. 13, line 34).

With respect to claim 22, the eukaryotic cell may be a yeast cell (col. 5, lines 9-12), the instantly elected transgenic cell/organism.

With respect to claims 23-24, Norris et al disclose the inducible promoter/operator genetic sequence is induced by an exogenous, non-toxic compound, e.g. isopropyl β-D-thiogalactopyranoside (IPTG) (col. 39, Example 6, lines 50-52).

With respect to Claim 25, those of ordinary skill in the art recognize that ccdB has anti-DNA gyrase activity, and that bacterial DNA gyrase and eukaryotic topoisomerase type II share the same CcdB binding structure. Thus, the yeast host cells inherently possess a genetic sequence that is or encodes the target [DNA topoisomerase type II] of the toxic molecule, absent evidence to the contrary.

With respect to claim 26, Norris et al contemplate a genus of eukaryotic expression vectors (col. 19, lines 1-57), including such genome integrative vectors as baculoviral vectors, tobacco mosaic viral vectors, Ti plasmids, and retroviral vectors (col. 25, lines 21-30), wherein said vectors integrate into the host chromosomal DNA, as well as non-integrating vectors (col. 25, lines 43-46).

Those of ordinary skill in the art have long understood that the retroviral integration enzyme confers site-specificity to the chromosomal nucleic acid sequence into which the retroviral nucleic acid integrates (Sandmeyer et al). Similarly, Ti plasmids have long been recognized to encode enzymes that confer site-specific integration (Yanofsky et al). Thus, those of ordinary skill in the art would immediately recognize that the eukaryotic expression vectors disclosed by Norris et al inherently confer site-specific integration.

With respect to Claim 28, as a first matter, neither the claims nor the specification define the selectable marker. Thus, any nucleic acid sequence between the first and second toxic genes is interpreted by the Examiner to reasonably fulfill the limitation because any such sequence may be selected, e.g. by polymerase chain reaction (PCR) or by restriction site, as per the artisan's desired methodology. As a second matter, the claim requires the selectable marker to be bordered by two different toxic genes. While the first toxic gene is required to encode a toxic protein selected from a poison protein/antidote group (Claim 15), neither the claims nor the specification require the toxic agent encoded by the second gene to also be a toxic protein selected from the poison protein/antidote group.

Norris et al disclose the genetic construct may comprise a first nucleic acid encoding a toxic protein and a second nucleic acid encoding another toxic gene product, e.g. a toxic antisense molecule (col. 8, lines 49-51; col. 15, lines 32-40), wherein a spacer nucleic acid sequence is used to link the toxic agents together (col. 10, lines 13-16). Such spacer elements are "selectable" because, for example, they may be subject to autocatalytically cleaving ribozymes also present in the genetic construct (col. 10, lines 24-43; col. 16, lines 5-27), whereupon the artisan would be able to select for those genetic constructs that functionally express both the first and second toxic gene products.

With respect to claim 34, the genetic construct comprises a selectable marker (col. 30, line 59; Example 7).

With respect to claim 35, the genetic sequence encoding the antidote is an episomal DNA, Norris et al contemplate a genus of eukaryotic expression vectors (col. 19, lines 1-57), including non-integrating vectors (col. 25, lines 43-46).

With respect to claim 36, the genetic construct comprises a genetic sequence encoding the antidote (col.3, lines 5-9; col. 13, lines 33-50), wherein those of ordinary skill in the art recognize that the Phd/Doc antidote/toxic protein system is transcriptionally coupled and the introduction of a promoter into the Phd/Doc operon would uncouple the antidote/toxic protein system.

With respect to Claims 41-42, Norris et al do not disclose *ipsis verbis* that the sequence encoding the toxic molecule is flanked by regions allowing homologous recombination, wherein the regions allowing homologous recombination are LB and RB repeats. However, those of ordinary skill in the art recognize that the genetic borders of Ti plasmids naturally possess LB and RB repeats (admitted by Applicant; specification, [0015], in reference to Hellens et al and Dennis et al).

Response to Arguments

Applicant argues that Norris et al do not disclose the genetic construct is incorporated in the genome of the host cell at a specific site.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant appears to have overlooked that Norris et al disclose the genetic construct may be delivered to the eukaryotic host cell via a retroviral vector that integrates into the host chromosomal DNA (col. 25, lines 21-26), wherein those of ordinary skill in the art have long understood that the retroviral integration enzyme confers site-specificity to the chromosomal nucleic acid sequence into which the retroviral nucleic acid integrates (Sandmeyer et al). Similarly, Ti plasmids have long been recognized to encode enzymes that confer site-specific integration (Yanofsky et al). Thus, those of ordinary skill in the art would immediately recognize that the eukaryotic expression vectors disclosed by Norris et al inherently confer site-specific integration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. **Claims 15-16, 22-24, 26 and 35 stand, and Claims 25, 34, 36 and 41 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (Appl. Environ. Microbiol. 66(12):5524-5526, 2000) in view of Parekh et al (Biotechnol. Prog. 12:16-21, 1996).

This rejection is maintained for reasons of record in the Office Action mailed December 12, 2007 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed June 10, 2008 and the petition decision dated April 28, 2009.

Determining the scope and contents of the prior art.

Kristoffersen et al teach a genetically modified yeast having a genetic construct comprising at least one nucleotide sequence comprising a toxic gene, specifically *relE*, under the control of an inducible promoter, specifically GAL1, whereupon expression of *relE* is induced by exogenous, non-toxic compound, galactose, said yeast further comprising a genetic sequence encoding an antidote molecule, specifically *relB*, wherein the art recognizes the prokaryotic *relB* as "not present natively" in yeast, and wherein the genetic sequence encoding the antidote molecule is under the control of an inducible promoter, specifically MET25, whereupon the expression of *relB* is induced by the absence of methionine (pg 5525, col. 1, last ¶), wherein the art recognizes the pYES2 expression vector to be an episomal DNA.

The genetic construct comprises a selectable marker, e.g. ura+ or ura+, met+ (pg 5524, Strains), as well as a nucleic acid sequence encoding the antidote (pg 5525, col. 1, last ¶). Kristoffersen et al teach that *relE* strongly inhibits the growth of yeast cells, and thus, absent

evidence to the contrary, the yeast host cells necessarily possess a genetic sequence that is or encodes the target of the toxic molecule.

Kristoffersen et al do not teach the genetic construct to be integrated into the genome of the host cell. However, at the time of the invention, Parekh et al taught the use of yeast transformation vectors that integrate into the yeast genome for stable transformation.

The Ty γ integration vectors are recognized in the art to possess long terminal repeats for integration by homologous recombination.

Ascertaining the differences between the prior art and the claims at issue.

When analyzed in light of the specification, the nature of the invention is the use of poison/antidote genetic systems, commonly used in prokaryotic host cell systems to facilitate cloning, in eukaryotic host cells, e.g. yeast cells. Prior to the invention, skilled artisans were well aware of integrating and non-integrating yeast transformation vectors. Furthermore, the use of a poison/antidote genetic system had been practiced in yeast cells.

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s, Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely have both the practical experience in molecular biology and the creation of transgenic cells and organism. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a non-integrating yeast transformation vector as taught by Kristoffersen et al with an integrating yeast transformation vector as taught by Parekh et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute an episomal transformation vector with an integrating transformation vector because the integrating vector would be stably and predictably propagated into each daughter cell.

Thus, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant argues that:

a) the vectors disclosed by Parekh et al produce multiple integrations which are not at a specific site;

b) a skilled artisan would not be motivated to combine the disclosure of Kristoffersen et al. with that of Parekh et al. Kristoffersen et al. relate to biological containment systems and does not suggest that integration of the poison protein would improve such systems. Parekh et al. relates only to integrative vectors for use with yeast. The Examiner contends that a skilled artisan would want to increase the effectiveness of the system disclosed by Kristoffersen et al. by integrating the sequence encoding the poison protein into the genome of the cell. Applicants, however, do not agree that integrating a sequence encoding a poison protein into the cell would improve the biological containment system disclosed by Kristoffersen et al. In fact, integration of a sequence encoding a poison protein into a host cell genome would prevent the elimination of the containment system when it is no longer desired or necessary. As such, the skilled artisan would not be motivated to modify the disclosure of Kristoffersen et al. in view of Parekh et al; and
c) Applicants submit that it is only through hindsight analysis that the Examiner applies the disclosure of Parekh et al. to that of Kristoffersen et al.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), Applicant appears to have overlooked that the integration site for the vectors of Parekh et al are Ty γ sites present in the host cell chromosome, wherein those of ordinary skill in the art recognize that Ty γ sites possess a specific consensus nucleic acid sequence, and wherein integration occurs by site-specific homologous recombination. That greater than one Ty γ sites exist in the host genome is irrelevant because the claim does not required a single integration of the genetic construct. Rather, the claim uses the open language "comprising" which reasonably allows for more than one genetic construct to integrate into more than one site-specific location, e.g. one or more of the Ty γ sites.

With respect to b), in response to Applicant's argument that a skilled artisan would not be motivated to combine the disclosure of Kristoffersen et al. with that of Parekh et al. because integration of a sequence encoding a poison protein into a host cell genome would prevent the elimination of the containment system when it is no longer desired or necessary, the fact that Applicant has recognized another advantage which would flow naturally from following the

suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In the instant case, the problem shared by both Kristoffersen et al and Parekh et al is the expression of heterologous nucleic acids in a eukaryotic host cell, wherein those of ordinary skill in the art have long-recognized that the heterologous nucleic acids may exist as an extra-chromosomal molecule or integrated into the host genome (Parekh). Furthermore, Applicant is respectfully reminded that the expression of the genetic construct is under the artisan's control (Kristoffersen et al) when it expression is no longer desired or necessary.

With respect to c), in response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the problem shared by both Kristoffersen et al and Parekh et al is the expression of heterologous nucleic acids in a eukaryotic host cell, wherein those of ordinary skill in the art have long-recognized that the heterologous nucleic acids may exist as an extra-chromosomal molecule or integrated into the host genome (Parekh), wherein Parekh et al teach a means for tunable, stable integration of a genetic construct into a eukaryotic host genome to overcome population heterogeneity and clonal variability.

10. **The prior rejection of Claims 15 and 18 under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (Appl. Environ. Microbiol. 66(12):5524-5526, 2000) and Parekh et al (Biotechnol. Prog. 12:16-21, 1996), as applied to claims 15-16, 22-24, 26 and 35, and in further view of Norris et al (U.S. Patent No. 6,271,359) **is withdrawn** in favor of the rejection set forth below.

11. **Claims 18, 28 and 42 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (Appl. Environ. Microbiol. 66(12):5524-5526, 2000) and Parekh et al

(Biotechnol. Prog. 12:16-21, 1996), as applied to claims 15-16, 22-26, 34-36 and 41, and in further view of Norris et al (U.S. Patent No. 6,271,359) and Pecota et al (Appl. Environ. Microbiol. 63(5):1917-1924, 1997; *of record in IDS, #89).

Determining the scope and contents of the prior art.

Neither Kristoffersen et al nor Parekh et al teach the toxic gene to be CcdB. However, at the time of the invention, Norris et al disclosed eukaryotic cells, e.g. yeast cells (col. 5, lines 9-12), the instantly elected transgenic cell/organism, comprising a genetic construct comprising at least one nucleotide sequence comprising a toxic gene, wherein said toxic gene is under the control of an inducible promoter, the eukaryotic cell further comprising an anti-toxic genetic sequence encoding an antidote molecule to the poison protein, wherein said antidote molecule is a heterologous ("not natively present") in said eukaryotic cell (col. 8, lines 35-39; col. 30, lines 46-50). The genetic sequence encoding the antidote molecule is under the control of an inducible promoter/operator genetic sequence (col. 6, lines 15-24; col. 8, lines 35-37; col. 29, lines 45-53) that is induced by an exogenous, non-toxic compound, e.g. isopropyl β-D-thiogalactopyranoside (IPTG) (col. 39, Example 6, lines 50-52). Norris et al contemplated a genus of eukaryotic expression vectors (col. 19, lines 1-57), including such genome integrative vectors as baculoviral vectors, tobacco mosaic viral vectors, Ti plasmids, and retroviral vectors (col. 25, lines 21-30), as well as non-integrating vectors (col. 25, lines 43-46). Furthermore, the genetic sequence encoding the antidote is an episomal DNA or non-integrating vectors (col. 25, lines 43-46). Norris et al disclosed the toxic gene CcdB (col. 13, line 34).

Norris et al do not disclose *ipsis verbis* that the sequence encoding the toxic molecule is flanked by regions allowing homologous recombination, wherein the regions allowing homologous recombination are LB and RB repeats. However, those of ordinary skill in the art recognize that the genetic borders of Ti plasmids naturally possess LB and RB repeats (admitted by Applicant; specification, [0015], in reference to Hellens et al and Dennis et al).

With respect to Claim 28, as a first matter, neither the claims nor the specification define the selectable marker. Thus, any nucleic acid sequence between the first and second toxic genes is interpreted by the Examiner to reasonably fulfill the limitation because any such sequence may be selected, e.g. by polymerase chain reaction (PCR) or by restriction site, as per the artisan's desired methodology. As a second matter, the claim requires the selectable marker to be bordered by two different toxic genes. While the first toxic gene is required to encode a toxic protein selected from a poison protein/antidote group (Claim 15), neither the claims nor the specification require the toxic agent encoded by the second gene to also be a toxic protein selected from a poison protein/antidote group.

Norris et al disclose the genetic construct may comprise a first nucleic acid encoding a toxic protein and a second nucleic acid encoding another toxic gene product, e.g. a toxic antisense molecule (col. 8, lines 49-51; col. 15, lines 32-40), wherein a spacer nucleic acid sequence is used to link the toxic agents together (col. 10, lines 13-16). Such spacer elements are "selectable" because, for example, they may be subject to autocatalytically cleaving ribozymes also present in the genetic construct (col. 10, lines 24-43; col. 16, lines 5-27), whereupon the artisan would select for those genetic constructs that functionally express both the first and second toxic gene products.

Similarly, Pecota et al teach the construction of a genetic construct comprising a first nucleic acid encoding a toxic protein and a second nucleic acid encoding second toxic protein, wherein the selectable marker is bordered by said first and second nucleic acids encoding toxic proteins (pg 1919, Figure 1, Plasmid maps).

Ascertaining the differences between the prior art and the claims at issue.

When analyzed in light of the specification, the nature of the invention is the use of poison/antidote genetic systems, commonly used in prokaryotic host cell systems to facilitate cloning, in eukaryotic host cells, e.g. yeast cells. Prior to the invention, skilled artisans were well aware of poison/antidote genetic systems, as well as their use in eukaryotic yeast cells.

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s, Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely have the practical experience in molecular biology, the creation of transgenic cells and organism and the use of poison/antidote genetic systems. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a relE/relB poison/antidote genetic system as taught by Kristoffersen et al with a CcdB/CcdA poison/antidote genetic system as taught by Norris et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute one poison/antidote genetic system for another as a matter of optimizing the transformation and stable propagation of a transformation vector in a desired eukaryotic cell type.

It also would have been obvious to one of ordinary skill in the art to substitute a first region allowing homologous recombination as taught by Parekh et al with a second region allowing homologous recombination, e.g. comprising LB and RB repeats as taught by Norris et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)." When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, those of ordinary skill in the art recognize that regions allowing homologous recombination are functional equivalents for the intended purpose of integrating site-specifically an exogenous nucleic acid into a host genomic nucleic acid molecule. An artisan would be motivated to substitute a first region allowing homologous recombination with a second region allowing homologous recombination because each region allowing homologous recombination is site-specific for different nucleic acid sequences, and depending upon the desired host genetic material to be targeted, the ordinary artisan would use the appropriate homologous recombination regions. A region allowing homologous recombination comprising LB and RB repeats would be applicable to the desired host cell and merely represents a design of choice as per the needs of the artisan.

It also would have been obvious to modify the poison/antidote expression system of Kristoffersen et al to comprise a selectable marker bordered by two different toxic genes as taught by Norris et al and/or Pecota et al with a reasonable expectation of success because both Norris et al and Pecota et al teach such a vector design and Pectoa et al successfully demonstrated the use of a dual toxic genes in a poison/antidote expression system. It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741,82 USPQ2d 1385, 1396 (2007). See also id. At 1742, 82 USPQ2d 1397 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). In the instant case, the placement of a selectable marker between

two toxic genes is an art-recognized design choice. An artisan would have been motivated to modify a poison/antidote expression system to comprise a selectable marker bordered by two different toxic genes because Pecota et al taught at least enhancing plasmid stability for a cloning vector by combining two pairs of independent post-segregational killing loci, in which the two loci are in the same or in opposite transcriptional orientations to each other.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

12. **The prior rejection of Claims 15 and 27 under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (Appl. Environ. Microbiol. 66(12):5524-5526, 2000), Parekh et al (Biotechnol. Prog. 12:16-21, 1996) and Norris et al (U.S. Patent No. 6,271,359), as applied to claims 15-16, 18, 22-24, 26 and 35, and in further view of Newman et al (Mol. Gen. Genet. 230(1-2):65-74, 1991; Abstract only) and Rochaix (Ann. Rev. Genet. 29: 209-230, 1995) **is withdrawn** in favor of the rejection set forth below.

13. **Claim 27 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (Appl. Environ. Microbiol. 66(12):5524-5526, 2000), Parekh et al (Biotechnol. Prog. 12:16-21, 1996) and Norris et al (U.S. Patent No. 6,271,359) and Pecota et al (Appl. Environ. Microbiol. 63(5):1917-1924, 1997; *of record in IDS, #89), as applied to claims 15-16, 18, 22-26, 34-36 and 41-42, and in further view of Newman et al (Mol. Gen. Genet. 230(1-2):65-74, 1991; Abstract only) and Rochaix (Ann. Rev. Genet. 29: 209-230, 1995).

Determining the scope and contents of the prior art.

Neither Kristoffersen et al, Parekh et al, nor Norris et al teach the genetic construct to be integrated into the chloroplast genome of the host cell. However, at the time of the invention, Newman et al taught the ability to genetically transform the chloroplast genome of the *Chlamydomonas reinhardtii* with an integrating transformation vector, wherein the art recognizes *C. reinhardtii* to be a photosynthetic yeast (Rochaix).

Ascertaining the differences between the prior art and the claims at issue.

When analyzed in light of the specification, the nature of the invention is the use of poison/antidote genetic systems, commonly used in prokaryotic host cell systems to facilitate cloning, in eukaryotic host cells, e.g. yeast cells. Prior to the invention, skilled artisans were well aware of poison/antidote genetic systems, as well as chloroplast transformation vectors and protocols in photosynthetic yeasts.

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s, Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely have the practical experience in molecular biology, the creation of transgenic cells and organism and the use of poison/antidote genetic systems. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a nuclear integrating transformation vector as taught by Norris et al with a chloroplast integrating transformation vector as taught by Newman et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute one integrating transformation vector for another as a matter of optimizing the transformation and stable propagation of a transformation vector in a desired eukaryotic cell type.

Thus, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant argues that neither Norris et al, Newman et al nor Rochaix et al remedy the defect of Kristoffersen et al in view of Parekh et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Kristoffersen et al in view of Parekh et al are discussed above and incorporated herein.

Applicant does not contest the teachings of Norris et al as applied to the obviousness to substitute a relE/relB poison/antidote genetic system with a CcdB/CcdA poison/antidote genetic system, nor the teachings of Newman et al and Rochaix et al as applied to the obviousness to substitute a nuclear integrating transformation vector with a chloroplast integrating transformation vector.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. **Claims 15-16, 18, 22-24, 26 and 35 (36) are provisionally rejected on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims 1-3, 9-10, 13-16 and 22 of copending Application No. 11/558,856 (U.S. 2008/0182327 A1; amendment filed April 6, 2009. A Notice of Allowance was mailed May 22, 2009.)

This is a new rejection.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the co-pending application reasonably embrace or are anticipated by the instant claims.

With respect to Claims 15, 16 and 26, the co-pending application claims (claim 1) a recombinant cell comprising a first nucleic acid sequence coding for a poison protein operably linked to a first regulatory sequence and a second nucleic acid sequence encoding an antidote to said poison protein operably linked to a second regulatory sequence, wherein the first nucleic acid sequence is located in the chromosome of the cell. The first regulatory sequence is an inducible promoter, inducible by an exogenous chemical compound (claims 14-16).

With respect to Claims 18, the toxic protein may be ccdB (claim 13), wherein those of ordinary skill in the art recognize that the ccdB toxic protein is derived from the *E. coli* F sex factor plasmid (claims 9-10).

With respect to Claims 22, the host cell is a yeast cell (claim 22).

With respect to Claims 23-24, the inducer is an exogenous chemical compound (claims 14-16), wherein the specification discloses said inducer may be a non-toxic compound, e.g. IPTG [0110].

With respect to Claims 35-36, the nucleic acid sequence encoding the antidote is in an episomal DNA (claim 3) or present in the chromosome (claim 2).

Thus, the recombinant cell comprising the recombinant nucleic acid molecule(s) in '856 are reasonably embraced and/or anticipated by the instantly claimed recombinant cell comprising the recombinant nucleic acid molecule(s).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

15. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633